Analysis of NTP Rodent Cancer Bioassay Data

Shyamal D. Peddada Biostatistics Branch NIEHS





Collaborators

- Dr. Joe Haseman
- Dr. Gregg Dinse
- Dr. Grace Kissling

Outline of the Talk

- Some motivating examples from NTP studies
- The new test statistic
- · The null distribution
- · Results from simulation studies
- Re-analysis of the NTP examples
- Conclusions

NTP Example 1

Methyleugenol (Male Rats)

• Tumor: Skin Fibroma

Dose (mg/Kg): 0 37 75 150
 Number of tumors: 1 9 8 5
 Poly-3 tumor rates: .02 .22 .21 .15

• P-value (NTP Poly-3 trend test): 0.11

NTP Example 2

Isoprene (Female Rats)

• Tumor: Mammary Gland Fibroadenoma

Dose (ppm): 0 220 700 7000
 Number of tumors: 19 35 32 32
 Poly-3 tumor rates: .43 .74 .74 .73

• P-value (NTP Poly-3 trend test): 0.11

NTP Example 3

Chloroprene (Female rats)

• Tumor: Alveolar/Bronchiolar Adenoma

Dose (ppm): 0 12.8 32 82
 Number of tumors: 1 0 0 3
 Poly-3 tumor rates: .024 0 0 .074

• P-value (NTP Poly-3 trend test): 0.06

Motivation for the New Trend Test

- The NTP trend test generally performs well when the trend is linear. However, it loses power as the pattern of response deviates from linearity.
- This motivates the new trend test which is almost as good as NTP's trend test for linear response and often performs significantly better for nonlinear patterns.

Poly-3 Isotonic Regression Test

Peddada, Dinse and Haseman (2005, *JRSS-C, to appear*)

Related articles:

Peddada, Prescott and Conaway (2001, *Biometrics*) Hwang and Peddada (1994, *Annals of Statistics*)

Some Notations

Let n_i^* denote the Poly - 3 adjusted sample size.

$$\hat{\pi}_i = \frac{Y_i}{n_i^*}, \ i = 1, 2, ..., k.$$

$$\widetilde{\pi}_1 = \min_i \left\{ \frac{\sum_{j=1}^{i} n_j^* \widehat{\pi}_j}{\sum_{j}^{i} n_j^*} \right\}, \qquad \widetilde{\pi}_k = \max_i \left\{ \frac{\sum_{j=1}^{k} n_j^* \widehat{\pi}_j}{\sum_{j=1}^{k} n_j^*} \right\}$$

(Pool Adjacent Violator Algorithm, PAVA)

Poly-3 Isotonic Regression Test

For
$$j^{th}$$
 animal in the i^{th} dose group, let
$$r_{ij} = Y_{ij} - \sum_{j} Y_{ij} N_{ij}, \quad \overline{r_i} = \sum_{j} r_{ij}, \quad N = \sum_{i} n_i,$$

$$S^2 = \frac{1}{N-k} N - k \quad , \quad N_{ij} \text{ is the associated Poly-3}$$
weight.

Define

$$W_{1} = \frac{\widetilde{\pi}_{k} - \widetilde{\pi}_{1}}{S\sqrt{\frac{n_{1}}{n_{1}^{*2}} + \frac{n_{k}}{n_{k}^{*2}}}}$$

Poly-3 Isotonic Regression Test

• Denote the NTP's trend test statistic by

$$W_2=g(\hat{\pi}_1,\hat{\pi}_2,...,\hat{\pi}_k)$$

· Then the proposed test statistic is

$$W = \max\left(W_1, W_2\right)$$

The null distribution of W

- For i = 1, 2, ..., k, let $Z_i \stackrel{iid}{\sim} N(0,1)$

$$W \stackrel{approximately}{\sim} \max \Biggl(rac{\hat{Z}_k - \hat{Z}_1}{\sqrt{2}}, \ g(Z_1, Z_2, ..., Z_k) \Biggr)$$

Comparison between *W* and NTP Poly-3 trend test : Simulation experiments

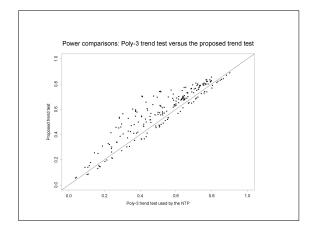
- As in Bailer and Portier (1988), Dinse (1994), etc. simulations were performed under Weibull models for incidence and mortality.
- 600 different non-null configurations and 120 different null configurations were considered.
 - tumor incidence ratios (6 different patterns)
 - background rates (4 different patterns)mortality rates (5 different patterns)
 - tumor onset shape parameters (3 patterns: 1.5,
 - dose patterns (2 patterns: 2-fold and 5-fold spacing)

False Positive Rate (Type I Error Rate)

No significant difference in the false positive rate between the two test procedures

Sensitivity (Power)

- Results for 2-fold dose spacing are summarized in the attached plot.
- Points above the diagonal correspond to the case where the proposed test is significantly better than NTP's Poly-3 trend test.
- Points below the diagonal correspond to the case where the NTP's Poly-3 trend test is <u>significantly</u> better than the proposed trend test.



Conclusions based on the Simulation Studies

- The proposed test enjoys larger power than NTP Poly-3 trend test in most situations.
 - Gains in power can be substantial:
 - in the best case it is 28% (for NTP Poly-3 trend test) versus 53% (for the proposed trend test).
 - Loss in power is minimal:
 - in the worst case it is 11% (for NTP Poly-3 trend test) versus 8% (for the proposed trend test).

Back to Example 1

Methyleugenol (Male Rats)

Tumor: Skin Fibroma

Number of tumors: 1, 9, 8, 5

P-value (NTP Poly-3 trend test): 0.110
 P-value (Proposed trend test): 0.027

· NTP's conclusion: Neoplastic effect

Back to Example 2

Isoprene (Female Rats)

• Tumor: Mammary Gland Fibroadenoma Number of tumors: 19, 35, 32, 32

P-value (NTP Poly-3 trend test): 0.110
 P-value (Proposed trend test): < 0.001

· NTP's conclusion: Neoplastic effect

 Note: The trend was significant in male rats too (P < 0.001).

Back to Example 3

Chloroprene (Female Rats)

• Tumor: Alveolar/Bronchiolar Adenoma Number of tumors: 1, 0, 0, 3

P-value (NTP Poly-3 trend test): 0.06
 P-value (Proposed trend test): 0.037

NTP's conclusion: Uncertain Effect

 NTP noted Male Rats and Mice and Female Mice had significant trends.

Summary of Some NTP Examples

Chemical	Tumor	Tumor incidence (Surv. Adj. Rates)	Poly-3 Trend trend P-value	Proposed test P-value	NTP conclusions	
(sex/species)					Neoplastic	
					effect?	
Methyleuginol						
(Male Rats)	Skin Fibroma	1, 9, 8, 5	0.11	0.027*	Yes	
(0, 37, 75, 150) mg/Kg		(.02, .22, .21, .15	i			
Turmeric Oleoresin	Hepat. Adenoma	7. 8. 19. 14	0.11	0.014*	Uncertain	
(Female Mice)		(.15184430				
(0, 2, 10, 50)x 1000 ppm		(10) 110) 111) 100				
Isoprene		19, 35, 32, 32	0.11	<0.001 **		
(Female Rats)	Fibroadenoma	(.43, .74, .74, .73)		Yes	
(0, 220, 700, 7000) ppm						
Chloroprene	Alveolar/Bronchiolar	1, 0, 0, 3	0.06	0.037*	Uncertain	NTP reported significant
(Female Rats)	Adenoma	(.024, 0, 0, .074)				trends in male rats
(0, 12.8, 32, 82) ppm						and mice and female mic
Hexachlorocyclopentadiene		0, 1, 3, 4	0.181	0.014*	No	
(Female Rats)	C-Cell Carcinoma	(0, .068, . 258, .086)			
(0, 0.01, 0.05, 0.20) ppm						